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TITLE: Development of a Hand Held Thromboelastograph

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CONTRACTING ORGANIZATION:

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14. ABSTRACT

The project objective is to develop a hand-held, ultra-portable thromboelastograph, ready for submission for FDA 510(k) clearance for clinical assessment of coagulation. Entegrion has designated the device as the *Portable Coagulation Monitor* (PCM). This research effort demonstrated the successful evaluation of the clot dynamics of untreated whole blood samples employing viscoelastic coagulation testing using the novel PCM technology. The PCM produced the results of these tests in the form of a graphic tracing of clotting activity consistent with thromboelastographs generated by other viscoelastic testing instruments currently in clinical use. The PCM technology completed the coagulation tests without the use of reagents or the need for pipetting samples, and using a low-cost instrument designed for ease of use, reduced operator to operator variability, resistance to vibration, humidity and temperature control, in a hand held form. The time to result was reduced as compared to existing viscoelastic coagulation testing instruments. Entegrion believes the PCM is well suited to accommodate additional types of tests on a single handheld platform based on the core PCM technology. Meetings with FDA have clarified the path to completion of a 510(k) premarket notification to the FDA.

15. SUBJECT TERMS
Coagulation monitor, thromboelastograph, viscoelastic coagulation testing, hemorrhage

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Table of Contents

INTRODUCTION

Trauma is known to induce hemostatic disorders such as trauma-induced coagulopathy (TIC), which evolves rapidly during the first few hours following injury. The limitations of routine tests of coagulation status, such as prothrombin time, offer limited utility in predicting bleeding from trauma or surgical procedures. Viscoelastic coagulation testing in which the dynamics of clot formation are examined in real time has become more widely used in acute care environments. However, commercially available instruments for performing these measurements have limitations that render these diagnostic instruments generally unsuitable for use in forward military treatment facilities and particularly during patient transport. Haemonetics' thrombelastography (TEG) and ROTEM thromboelastometry (TEM)) instruments require clean, stable, vibration-free environments to properly perform these measurements, and coagulation assessments using these instruments can take up to an hour. Entegrion has developed an alternative to the existing solutions that will perform viscoelastic coagulation testing using a portable handheld instrument suitable for far forward and patient transport arenas, and has designated this new technology as the *Portable Coagulation Monitor* (PCM). Use of this device will allow surgeons in level 1, 2, or 3 hospitals to make medical decisions based on the accepted state of a patient's coagulation profile. The project objective is to develop a hand-held, portable thromboelastograph suitable for 510(k) submission to the FDA.

KEYWORDS

Coagulation monitor, thromboelastograph, viscoelastic coagulation testing, hemorrhage.

OVERALL PROJECT SUMMARY

Project Objective

The primary objective of the project was to develop a prototype hand-held portable device that replicates the basic functionality of commercially available viscoelastic coagulation testing systems (TEG and ROTEM), but with greatly improved portability, and the ability to perform this diagnostic test at the point of patient care under a variety of environmental conditions. Prior to the initiation of this research project, Entegrion had designed a novel technology now embodied in the PCM to approach this problem, and had investigated its initial feasibility.

Methods and Standards Used

With the goal of developing a diagnostic device suitable for submission to FDA for market clearance, the development, design, and manufacture of the PCM Device was performed in compliance with ISO 13485 and the FDA Quality System Regulation 21CFR Part 820. In addition, the following applicable standards and guidance documents will be referenced during the Entegrion PCM System design, verification and validation activities.

EN 61010-1:2010 (Edition3.0)	Safety requirements for electrical equipment for measurement, control, and laboratory use – Part 1: General requirements.
EN 61010-2-101:2002	Safety requirements for electrical equipment for measurement, control and laboratory use- Part 2-101: Particular requirements for in vitro diagnostics (IVD) medical equipment.

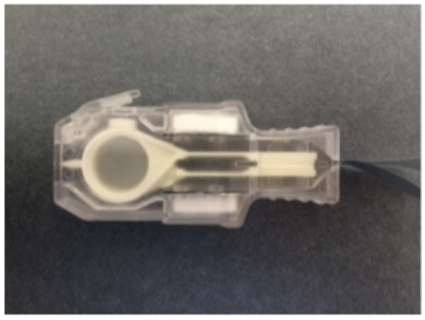
EN 61326-1:2013	Electrical equipment for measurement, control and laboratory use- EMC requirements- Part1: General requirements.
EN 61326-2-6:2006	Electrical equipment for measurement, control and laboratory use- EMC requirements- Part2-6: General requirements-In vitro diagnostic (IVD) medical equipment
EN 60601-1-6:2010	General Requirements for Basic Safety and Essential Performance--Collateral Standard: Usability.
IPC-A-610E	Acceptability of Electronic Assemblies
IPC 7711/21B	Rework, Modification and Repair of Electronic Assemblies.
IEC 62304:2006/AC:2008	Medical Device Software- Software Life Cycle Processes
IEEE 1233-1998	Guide for Developing System Requirements
BS EN 50419:2006	Marking of electrical and electronic equipment in accordance with article 11 (2) of Directive 2002/96/EC (WEEE)
BS EN 50581:2012	Technical documentation for the assessment of electrical and electronic products with respect to the restriction of hazardous substances
EN 62133:2013	Secondary cells and batteries containing alkaline or other non-acid electrolytes. Safety requirements for portable sealed secondary cells, and for batteries made from them, for use in portable applications
ISBN: 1 74186 158 6	Requirements for the Development and Use of In Vitro Diagnostic Devices (IVDs) (2007 Edition).
Directive 98/79/EC	In Vitro Diagnostic Medical Devices
ISO 9001:2008	Quality management systems- Requirements
ISO 13485:2012	Medical Device Quality Management Systems Requirements for Regulatory Purposes
EN 13612:2002	Performance evaluation of in vitro diagnostic medical devices
EN 13640:2002	Stability testing of in vitro diagnostic reagents
EN 13975:2003	Sampling procedures used for acceptance testing of in vitro diagnostic medical devices - Statistical aspects
ISO 14971:2012	Application of Risk Management to Medical Devices
ISO 15223-1:2012	Medical devices. Symbols to be used with medical device labels, labeling, and information to be supplied. Part 1: General requirements
BS EN ISO/IEC 17050-1	Conformity assessment. Suppliers declaration of conformity. General requirements.
EN ISO 18113-1:2011	In vitro diagnostic medical devices - Information supplied by the manufacturer (labelling) - Part 1: Terms, definitions and general requirements (ISO 18113-1:2009)
EN ISO 18113-2:2011	In vitro diagnostic medical devices - Information supplied

	by the manufacturer (labelling) - Part 2: In vitro diagnostic reagents for professional use (ISO 18113-2:2009)
EN ISO 18113-3:2011	In vitro diagnostic medical devices - Information supplied by the manufacturer (labelling) - Part 3: In vitro diagnostic instruments for professional use (ISO 18113-3:2009)
EN 62366:2008	Application of Usability Engineering for Medical Devices
ASTM D4169-:2001	Standard Practice for Performance Testing of Shipping Containers and Systems

Instrument Design

Prototype instruments were developed designed to be rugged, handheld, and portable. The PCM system has three basic components: (1) the user interface, (2) a blood sample cassette, and (3) the base PCM system (main control unit). The PCM system uses 125 µL of whole blood per sample. The sample of untreated venous blood is collected by introducing several drops of blood into a sample introduction cup on the sample cassette, and the blood is taken up into and covers the lenses of the cassette via capillary action between two glass capillary plates. The coagulation and thromboelastogram is generated by measuring the viscosity changes between the two glass capillaries in a shear mechanical test (similar to traditional viscometry). The system is approximately 7.5" x 5.0" x 1.0" in size and shape, and is designed to be portable. A touchscreen LCD screen is integrated into the system for data display. Images of the PCM analyzer and disposable test cartridges are provided below.

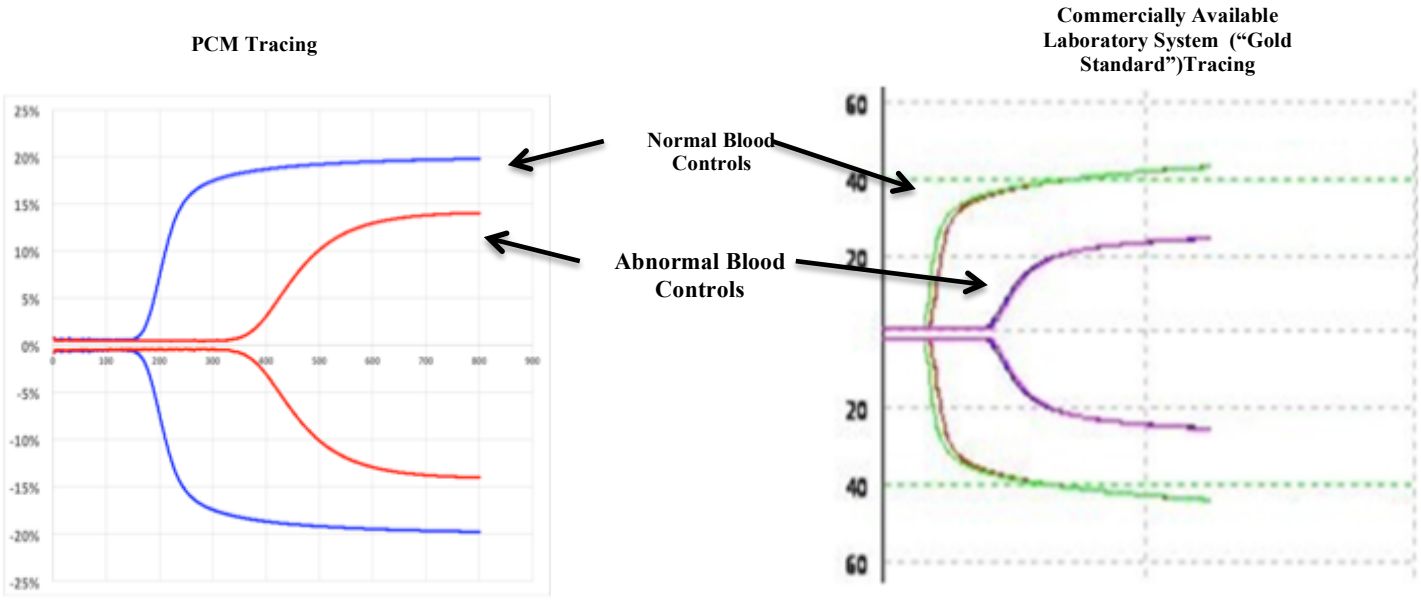
PCM Prototype Designed for Military Use



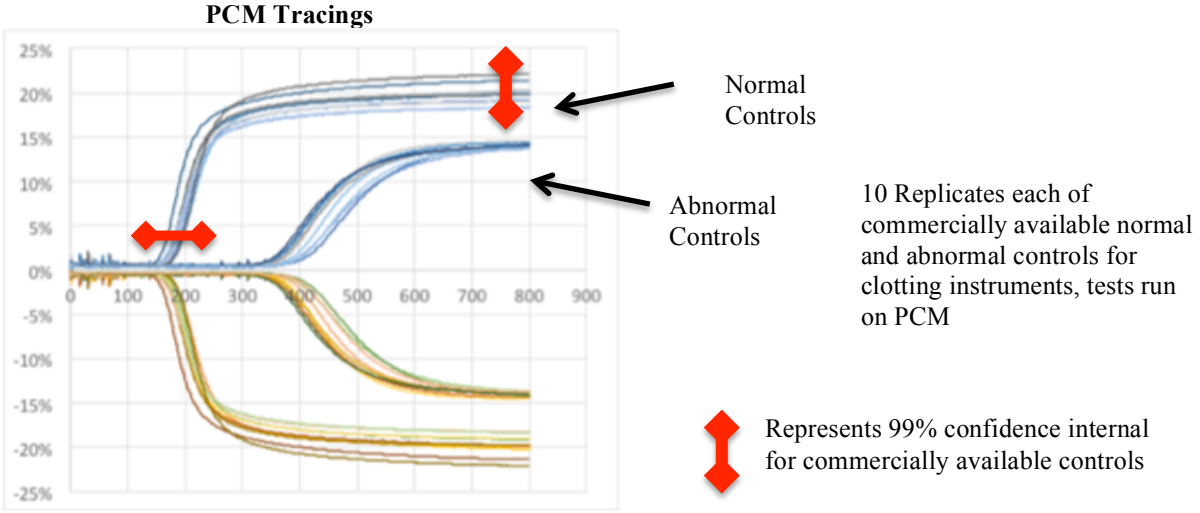
Disposable Sample Cartridge

Summary of Key Research Findings

The PCM system was developed to reliably produce a graphical tracing of clotting activity that is consistent with the results obtained using the same blood sample analyzed using a Rotem delta instrument. In addition to whole blood samples, control materials used to simulate the clotting characteristics of normal and abnormally clotting blood were evaluated using both the PCM and the Rotem delta instruments. Examples of the graphical output from those tests are shown below.

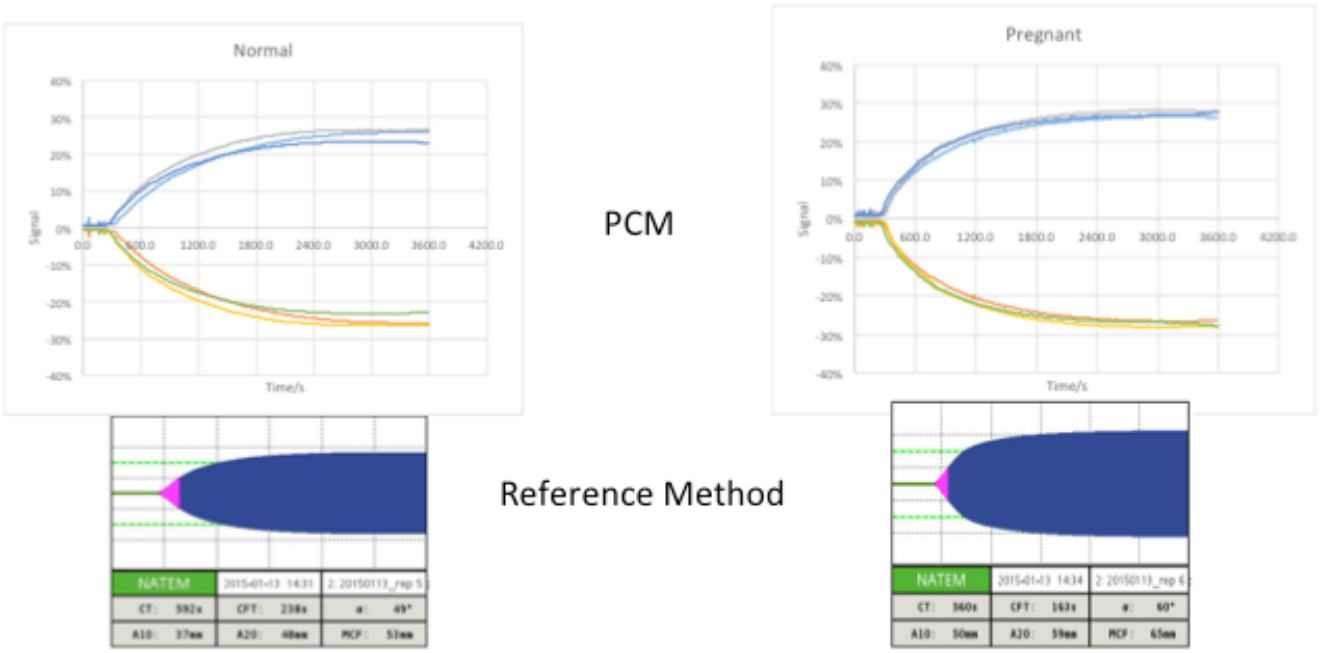


The images above illustrate the output from a viscoelastic coagulation test using human plasma control material with PCM on the left, and its comparability to the "gold standard" reference method tracing on the right. It is notable that the relationship between normal and abnormal diagnosis is comparable between the two systems. In this example the PCM demonstrates higher sensitivity than the other system. The tracings shown below from running multiple samples of a commercially available human plasma control material demonstrate the reproducibility of PCM results.



The above graphical output from multiple tests of control materials illustrates the reproducibility of PCM results. In this example, the 10 replicates using PCM to evaluate the coagulation activity indicated by commercially available controls produced substantially the same results.

The PCM has been evaluated on whole fresh venous blood and compared to the reference method. The example tracings below demonstrate that the PCM output is analogous to the reference method, and demonstrate that the technology will detect subtle differences in thromboelastogram profiling.



Entegrion previously reported that due to the inadequate performance of the engineering subcontractor initially engaged to develop the first PCM prototypes, the project was delayed and extensive testing of the device and its design was not possible because the prototype devices were unreliable. Entegrion subsequently engaged a second subcontractor that implemented extensive design modifications. Key variables affecting the performance of the test and the solution are described below.

Humidity Control

Because of the small volume of blood used in the PCM assay and the avoidance of the use of reagents, the blood sample has an opportunity to dry if humidity is not controlled, thus distorting the test results. This is particularly the case if capturing fibrinolysis activity during the test is deemed important, a process that requires an extended time to measure. The challenge of sample drying is a known problem with other viscoelastic coagulation testing systems in use. In addition, the PCM is intended to be used under a variety of environmental conditions, including in the field, that may contribute to blood sample drying. Humidity control was thus introduced into the sample cartridge, and resulted in improved test reliability.

Temperature Control

Blood coagulation is affected by changes in the ambient temperature in which the test is performed. The PCM analyzer is equipped with an internal heating element to maintain the temperature of the sample.

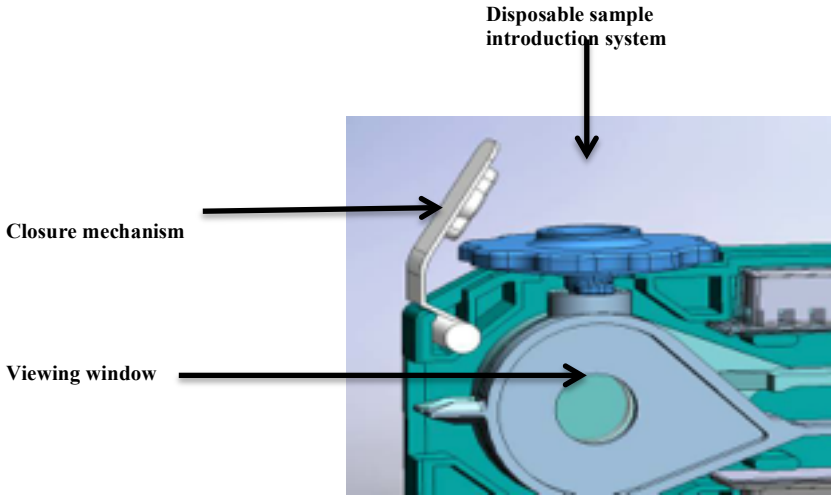
Instrument Sensitivity

Following extensive testing certain PCM components were determined not to be sufficient to attain the desired level of sensitivity. Additional research into resistance inherent in the original components

resulted in replacement of the voice coil motors in favor of ceramic motors and an alternative measurement mechanism to detect clotting activity, among other components.

Sample Loading

During testing it was recognized that a key contributor to reliable test results was the ability to consistently load blood samples into the reaction area of the test cartridge. Proper sample loading is also necessary to avoid operator and instrument contamination. Pipetting of samples needed to be avoided for ease of operation. These factors resulted in modifications to the disposable cartridge to add a blood introduction system on the cartridge in the form of a removable funnel to facilitate accurate sample loading. The blood introduction system used in the disposable cartridge obviates the need for the operator to measure the exact amount of blood to be used in the test cartridge. The schematic below illustrates this feature.



FDA Requirements

During this project Entegrion held two pre-submission meetings with FDA to obtain feedback on the development path for PCM. In the first of those meetings the FDA required a clinical study that was not anticipated, in addition to the planned reference range study. Due to the length of time required to implement modifications to the PCM instrument, the development team met again with the FDA in November 2014 to update FDA regarding the development of the device, and to receive any further input from FDA. In the November 2014 meeting, the FDA added several additional requirements beyond those addressed in their 2012 meeting, the most notable of which are the following:

1. Liquid controls – While Entegrion proposed that only a mechanical QC apparatus was needed for PCM because of its primarily mechanical approach to monitoring clotting activity, the FDA required that Entegrion develop liquid biologic controls for ensuring instrument calibration similar to the control material used by the Rotem delta instrument. This control material will be required to be validated specifically for PCM, and although the development team has identified a source for the material, this process will require until approximately July 2015 to complete, and will be required for 510(k) filing.

2. Clinical Study Modifications – The FDA stated that because clinicians rely on graphical representations of clotting activity in addition to numeric values provided by viscoelastic coagulation testing instruments, a separate study should be completed in which clinicians other than those conducting the method comparison (clinical) study compare blinded PCM graphical displays to the displays created by the predicate product for the same patients. Entegrion is developing the protocols to complete this portion of the study.

3. Nonclinical Study Modifications – The FDA also suggested modifications to the nonclinical laboratory studies that are being implemented now.

4. Cleaning Procedures – The FDA requires validation of the cleaning procedures and efficacy of microbial (bacterial and viral) removal from the PCM. These extensive study requirements are a relatively new focus of the FDA, and were not anticipated.

These various changes to the PCM development plan have delayed the expected submission date of the 510(k) pre-market notification to the FDA until approximately August 2015. Entegrion is continuing work on the matters noted above and has plans to submit the 510(k) as soon this work is complete. The remainder of this project is being funded through Entegrion investor resources.

KEY RESEARCH ACCOMPLISHMENTS

1. The research demonstrated that the PCM technology is capable of reliably producing viscoelastic coagulation testing results in the form of a thromboelastograph in a handheld and relatively low cost form factor. The PCM demonstrates substantial equivalence to commercially available laboratory viscoelastic testing instrument.
2. Methods to control the test environment (temperature, humidity, vibration) to facilitate viscoelastic coagulation testing in a portable test platform were proven effective.
3. The regulatory path to a commercially available hand held point of care thromboelastograph have been clarified by the FDA.
4. This research has enabled a full measurement of fibrinolysis previously not considered possible for the PCM. The evaluation of fibrinolysis is particularly relevant to the treatment of trauma patients, such as those inflicted with combat casualties.

CONCLUSION

This research will lead to the commercial availability of a handheld point of care viscoelastic coagulation testing instrument in an easy to use form. Entegrion believes the availability of this instrument will reduce turn around time and contribute to more rapid clinical interventions and improved patient outcomes. Entegrion plans to pursue FDA market clearance for the PCM during the coming months.

PUBLICATIONS, ABSTRACTS, AND PRESENTATIONS

None.

INVENTIONS, PATENTS, AND LICENSES

The following table sets forth issued patents and patent applications related to this technology. The application for the method of use patent issued by the USPTO in May 2013 was first filed prior to the initiation of the project that is the subject of this report. That patent is included here for reference.

Inventors	Title	Application Number	Filing Date	Patent Number	Issue Date	Jurisdiction
DaCorta, Fischer, Dennis	Portable Coagulation Monitoring Device and Method of Assessing Coagulation Response	12/971,013	Based on US provisional application # 61/287,780 filed Dec. 18, 2009.	8450078	5/28/13	United States
DaCorta, Fischer, Dennis	Portable Coagulation Monitoring Device and Method of Assessing Coagulation Response	2010234607	9/27/11	2010330861	5/1/14	Australia
DaCorta, Fischer, Dennis	Portable Coagulation Monitoring Device and Method of Assessing Coagulation Response	2012-103321	6/20/12	4003	9/18/13	Columbia
DaCorta, Fischer, Dennis	Portable Coagulation Monitoring Device and Method of Assessing Coagulation Response	201080055503.90	6/7/12	. 2010 8 0055503	7/16/14	China
DaCorta, Fischer, Dennis	Portable Coagulation Monitoring Device and Method of Assessing Coagulation Response	2012-544860	6/12/12	5655091	11/28/14	Japan
DaCorta, Fischer, Dennis	Portable Coagulation Monitoring Device and Method of Assessing Coagulation Response	739.1	6/18/12	739.12	11/13/12	Belize

Patent applications for this technology are pending in Europe, Canada, Ecuador, Peru, Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua, and Hong Kong.

REPORTABLE OUTCOMES

Presentation of PCM development program to Military Health System Research Symposium August 2013.

OTHER ACHIEVEMENTS

None

REFERENCES

None

APENDICES

None